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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 07/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/772,374	GASTON ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 1 AND 9 ARE PRESENTED FOR EXAMINATION

Applicants' "Amendment and Response to the January 31, 2006 Office Action", which includes a Terminal Disclaimer and a declaration under 37 C.F.R. § 1.132 by Drs. Jonathan S. Stamler and Benjamin Gaston, ("the Stamler et al. declaration), filed on May 2, 2006, has been received and entered into the application.

In view of the propriety of the above referenced terminal disclaimer, the rejection of claims 1 and 9 under the judicially-created doctrine of obviousness-type double patenting over claims 1, 2, 14 and 15 of U.S. Patent No. 6,627,602, (Stamler et al.), as maintained in the previous Office action dated January 31, 2006 at pages 5-6, is *withdrawn.*

It should be noted that in the rejection which follows, the Examiner has taken a position consistent with, but differing from that in the parent application. Great care has been taken in this matter and the rejection is being maintained based on consideration of the facts currently before the Examiner.

Claim Rejection - 35 USC § 103

Claims 1 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Garvey et al., (U.S. Patent No. 6,331,543) in view of Stamler (U.S. Patent No. 6,314,956; "Stamler '956"), each of record, for the reasons of record as set forth in the previous Office action dated January 31, 2006 at pages 3-5, which reasons are here incorporated by reference, and further in view of Stamler et al. (U.S. Patent No. 5,380,758; newly cited by the Examiner "Stamler '758").

New Grounds of Rejection Not Necessitated by Amendment

To buttress the above reasons for determining the claimed subject matter to have been obvious, it is further noted that Stamler '956 establishes that ethyl nitrite was a known NO donor compound, (see col. 3, line 66) and such knowledge would have motivated one of ordinary skill in the art to employ it in the manner taught by Garvey et al. for NO donating compounds in the treatment of cystic fibrosis. Further motivating a person of such skill in the art to employ ethyl nitrite, or compounds that provides NO once introduced into the body, such as organic compounds having the formula CF_3SNO, CH_3SNO, CH_2=CHSNO, etc., (Stamler '956 at col. 4, lines 1-5), would have been the fact that Stamler '956 further highlights that cystic fibrosis may be treated using such NO donating compounds, (e.g., see col. 3, lines 31-32 and lines 49-50 "Cystic fibrosis is associated with smooth muscle constriction in the lungs and can be associated with hypoxemia"). This teaching is particularly relevant and further renders the claimed subject matter obvious when taken with the teachings in Garvey et al. that "NO and NO donors have also been implicated as mediators of nonvascular smooth muscle relaxation", (emphasis added), (col. 3, lines 2-3). Additionally, it is noted at col. 9, Example V of Stamler '956, of a report of a 12-year old white female with *cystic fibrosis* given inhaled ethyl nitrite at 80 ppm with resolution of the infection she had been suffering from in four days.

In addition to the above, Stamler '758 is newly relied on to further establish the obviousness of employing a NO donating compound for the treatment of cystic fibrosis. As required in present claim 9, the amelioration of an exacerbation of mucus plugging is required. Such would have been obvious given the teaching in Stamler '758 that S-nitrosothiol compounds, such as S-nitroso-glutathione, (col. 5, line 13), may be used for the treatment of

cystic fibrosis, (col. 6, lines 55-60), and that an S-nitroso-thiol compound, such as S-nitroso-N-acetylcysteine, may advantageously be used to provide for both mucolytic and bronchodilatory activity, (col. 8, line 66 – col. 9, line 6). Stamler '758 provides for the use of further N-nitroso-thiol compounds for their mucolytic properties, (col. 9, lines 7-18).

Accordingly, in view of the above, the claims are deemed properly rejected.

Applicants' Remarks

Applicants' remarks at pages 3-5 of the above referenced response, as well as the Stamler et al. declaration, have been carefully considered, but fail to persuade the Examiner of error in his determination of obviousness.

In particular, in traversing the above rejection, Applicants have argued that while Garvey et al. specifically name "cystic fibrosis" as a disease amenable to treatment, such would not have been accepted by one of ordinary skill in the art because there would not have been a reasonable expectation of success in practicing this aspect of Garvey et al.'s disclosure, (see pages 3-4 of Applicants' response). In support of this position, Applicants offer that (i) Garvey contains no working examples directed to the treatment of a patient with cystic fibrosis, (ii) Garvey does not point to any specific compounds or compositions to treat cystic fibrosis thus having the artisan to select "a specific alternative where NO is used and one must select cystic fibrosis for a disease to treat; (iii) claim 66 of Garvey does not include cystic fibrosis among the disorders listed; and (iv), as supported by the Stamler et al. declaration, Garvey has incorrectly described cystic fibrosis as being a disease induced by increased metabolism of cGMP, (see Applicants' response at pages 4-5).

The above remarks of Applicants have been given due consideration, but are not seen to diminish the propriety of the present rejection for the following reasons.

While Garvey et al. contains no working example of the treatment of cystic fibrosis, the Examiner knows of no legal or administrative authority, and Applicants have not pointed to such an authority, which requires a reference to disclose a working example, (i.e., such as Example V in Stamler '956), in order to be relied on for concluding obviousness. Rather, as per MPEP §2164.02,

> "Compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.' A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.".

Applicants have remark that "Garvey does not point to any specific compound or compositions to treat cystic fibrosis. Thus, for Garvey to treat cystic fibrosis with an NO donor, one or (sic) ordinary skill in the art must select a specific alternative where NO is used and one must select cystic fibrosis for a disease to treat.", (response at page 4). This is not persuasive because Garvey does not disclose either an NO donor or cystic fibrosis in a veiled or nebulous manner. Clearly , both the Examiner and Applicants were able to not only find, but to understand each of these concepts as disclosed by Garvey. Also, that other compounds and diseases are disclosed by Garvey is not indicative of something that has not been either enabled or identified. As to this point, MPEP § 2131.02 is particularly germane where it is stated:

> "A genus does not always anticipate a claim to a species within the genus. However, *when the species is clearly named, the species claim is anticipated no*

> *matter how many other species are additionally named*. *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. The Board held that *the comprehensiveness of the listing did not negate the fact that the compound claimed was specifically taught.* The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that "the tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of those compounds is described' as that term is used in 35 U.S.C. § 102(a), in that publication."(emphasis added).

Thus having been named, each concept of an NO donor and cystic fibrosis was therefore in the possession of the public and also enabled because "A reference contains an 'enabling disclosure' if the public was in possession of the claimed invention before the date of invention. 'Such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985), (MPEP § 2121.02). Respecting the "with his [or] her own knowledge to make the claimed invention" requirement as indicated above, it is most assuredly within the skill of the artisan, having knowledge of the disease condition and the active agent, to then proceed the one step further of administering the agent to a patient suffering from the disease in order to practice the invention. Such a step is basic to the art of medicine.

Applicants have further argued that cystic fibrosis does not appear in the claims of the reference, i.e., in claim 66. This fails to diminish the propriety of the present rejection because the reference is not constituted solely of claims. As is clear from a reading of the reference as a whole, the expression "cystic fibrosis" appears five (5) times, (see the abstract; col. 1, lines 40-

41; col. 2, line 48; col. 4, line 67; col. 54, line 19; and col. 57, line 39). Also, why the disease does not appear in the claims is of no importance to the present issue. As established above by the Examiner, this disease state is properly enabled. Any matters existing before the status of the reference as a U.S. Patent is not in the purview of the Examiner as the present preceding is neither one of reissue, reexamination or interference, (see MPEP § 1701).

Finally, Applicant has argued that because Garvey has incorrectly identified cystic fibrosis as being a disease induced by cGMP, the presently claimed subject matter would not have been obvious. The Examiner is not persuaded by the point because whether or not cystic fibrosis is a disease actually induced by cGMP, one of ordinary skill in the art would have nevertheless appreciated, or else have been imbued with at least a reasonable expectation, that the NO donors would be effective in the treatment of cystic fibrosis. In assessing the teachings of Garvey, one of ordinary skill in the art would not have been limited to the teachings of the reference, but also to the totality of knowledge possessed thereby. In Garvey, the NO donor is not disclosed as affecting cGMP levels in any manner and thus, the accuracy of the patentees statement regarding cGMP inducing cystic fibrosis would not have been a "make or break" teaching to the artisan in practicing the invention described in Garvey. Indeed, the artisan's knowledge would have extended at least to the other references relied on by the Examiner, (i.e., Stamler '956 and '758), especially the teachings in such references where it is indicated that NO donating compounds of the type claimed may be used for the treatment of cystic fibrosis.

Declaration under 37 C.F.R. § 1.132 of Stamler et al.

In considering the statements made in the Stamler et al. declaration, the Examiner's above position remains as stated. In the Stamler et al. declaration, the declarants have averred

that (i) cystic fibrosis is not associated with vasoconstriction, (or constriction of the corpus cavernosum which is not seen germane to the present issue which does not involve an evaluation of effects on erectile dysfunction); (ii) cystic fibrosis is not known to be induced by the increased metabolism of cGMP; (iii) increased levels of cGMP are not known to be beneficial for amelioration of cystic fibrosis symptoms; (iv) endogenous levels of EDRF [endothelial derived relaxing factor] relate to vascular function and not to symptoms of cystic fibrosis; and (v) being familiar with Garvey, it is the point of Garvey to provide an increased level of cGMP to relax blood vessels or corpus cavernosum, (note the declaration at page 2).

Having carefully considered declarant's statements as well as the references relied on by the Examiner, the Examiner cannot afford the significance urged by Applicants to the declaration in rebutting the Examiner's conclusion of obviousness. In particular, The declaration under 37 CFR § 1.132 filed is insufficient to overcome the rejection of claims 1 and 9 as set forth above because:

(i) the statements regarding the corpus cavernosum, (i.e., statements "i" and "v" above) are not commensurate in scope with the claimed subject matter which does not include an element of treatment involving the penis or male sexual dysfunction;

(ii) the statements are conclusory in nature and not supported by fact, e.g., at least a cursory review of the etiology, pathophysiology and recognized treatments of cystic fibrosis, (i.e., statements i-v above);

(iii) the statements respecting the effects of increased cGMP metabolism or of cGMP itself, (see i, ii and iii, above) do not address the entire teachings in Garvey regarding NO donors, (e.g., Garvey teaches that "NO and NO donors have also been implicated as mediators of

nonvascular smooth muscle relaxation", (col. 3, lines 2-3), [this statement is not solely directed to the corpus cavernosum because this tissue is mentioned in an exemplary manner, "...this [smooth muscle relaxation] effect ***includes*** the dilation of the corpus cavernosum smooth muscle...", (col. 3, lines 4-5)], and do not address the smooth muscle relaxing effects of PDE inhibitors, (i.e., "The smooth muscle relaxant properties of phosphodiesterase inhibitors...", (col. 3, lines 17+));

(iv) declarants' statements that cystic fibrosis is not associated with vasoconstriction or constriction of the corpus cavernosum and cystic fibrosis is not known to be induced by the increased metabolism of cGMP) amount to affirmations that the declarants have never seen or not been aware of such matters which do not equate to an objective showing of proof.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence and arguments of nonobviousness fails to outweigh the evidence of obviousness. Accordingly, the claims remain properly rejected.

None of the claims are currently in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Raymond J Henley III
Primary Examiner
Art Unit 1614

July 8, 2006